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Xanthine Oxidase and Uric Acid in Cardiovascular Disease: Clinical Impact and Therapeutic Options

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Abstract

The association between increased uric acid (UA) levels and cardiovascular disease (CVD) has been observed and studied for many decades. The value of UA as an independent factor within the metabolic risk profile for prediction of CVD in the normal population remains an issue of ongoing discussion. In turn, increasing evidence suggests that among patients with established CVD such as heart failure UA is an independent marker of disease state and prognosis. Increased UA levels may be an indicator of up-regulated activity of xanthine oxidase, a powerful oxygen radical– generating system in human physiology. Increased reactive oxygen species (ROS) accumulation contributes to endothelium dysfunction, metabolic and functional impairment, inflammatory activation, and other features of cardiovascular pathophysiology. Accordingly, inhibition of xanthine oxidase activity has been shown to improve a range of surrogate markers in patients with CVD, but this effect seems to be tailored to hyperuricemic patients because disappointing results were reported in studies with normouricemic patients. In this review we summarize current evidence on hyperuricemia in CVD. The value of UA as a biomarker and as a therapeutic target for tailored metabolic treatment in CVD is discussed.

It has been observed for more than 50 years that hyperuricemia is associated with cardiovascular disease (CVD). Increased uric acid (UA) levels are a common observation in patients with CVD and a wealth of data have been accumulated that address UA as a cardiovascular risk factor. In fact, hyperuricemia is closely associated with hypertension, insulin resistance,[1] and other metabolic derangements (for review see Feig et al[2]). Accordingly, hyperuricemia has been added to the insulin resistance syndrome,[3] a cluster of metabolic abnormalities that are addressed clinically as metabolic syndrome. The discussion continued, however, as to whether UA is truly an independent predictor of coronary heart disease (CHD) or merely an embedded component within this metabolic syndrome. Many analyses have addressed this issue in prospective studies, registries, surveys, and cohort studies that cannot be discussed here in detail. A recent prospective study in 6,418 subjects plus a meta-analysis of 16 studies with a total of 9,458 patients with incident CHD and 155,084 controls found no convincing independent impact of UA. The odds ratio for patients in the top third compared with the bottom third of UA levels was 1.13 (95% confidence interval [CI], 1.07-1.20) in the total study population (males, 1.12; 95% CI, 1.05-1.19; females, 1.22; 95% CI, 1.05-1.40) to develop CHD in the subsequent decade. This ratio was reduced to a nonsignificant result of 1.02 (95% CI, 0.91-1.14) in the eight studies in which more complete adjustment for relevant confounders was possible.[4] The conclusion from these results was that serum UA levels are unlikely to be a major determinant of CHD and may not contribute importantly to the prediction of CHD in the general population. However, the discussion is ongoing because contrasting data also recently have been reported that observed UA as indeed a significant prognostic marker of cardiovascular events including myocardial infarction, heart failure, stroke,[5] and cardiovascular death.[6] In specific patient populations UA nevertheless may carry predictive information such as in stroke survivors, in whom a threefold increased risk for cardiac death was observed regardless of the use of diuretics and after adjustment for age, sex, and several metabolic confounders. [7] In addition, in patients with increased risk of or with established CHD disease UA was observed to predict prognosis.[8,9] In patients with heart failure there is substantial evidence that increased UA levels are highly predictive of increased morbidity and mortality both in acute and chronic diseased patients. This is discussed in the next section.

HYPERURICEMIA IN CONGESTIVE HEART FAILURE: DISEASE SEVERITY AND MORTALITY

Hyperuricemia is a common observation in patients with congestive heart failure (CHF) and an association with disease severity according to New York Heart Association functional class[10] or with symptomatic impairment in exercise capacity has been observed.[11] Notably, in these CHF patients, hyperuricemia does not depend on the presence of a metabolic syndrome risk profile for ischemic heart disease. Patients with ischemic and nonischemic heart failure showed a similar distribution of UA levels according to New York Heart Association classes. UA levels also were observed to carry powerful prognostic information in patients with CHF. Increased risk of all-cause death was observed in a dose-dependent relationship with hyperuricemia with as much as an 18-fold increased risk in those patients with UA levels greater than 800 µmol/L (Fig. 1).[12] The prognostic significance of high UA levels was independent of other established prognostic factors in CHF and added predictive power to established prognostic models such as the heart failure survival score.12 A recent large case-control analysis studied more than 25,000 patients (mean age, 77 y; median follow-up period, 2.1 y) who were discharged from the hospital with the recent diagnosis of heart failure.[13] A history of gout or an acute gout episode were independent risk factors for increased mortality or hospital re-admission for heart failure. In turn, the use of allopurinol improved outcome in these patients. Other studies also have shown similar results in patients with moderate heart failure (HF)[14] and in those with acute HF.[15,16] Accordingly, UA level has been included as independent factor in the Seattle Heart Failure Survival Score.[17] Moreover, a recent study in nonischemic heart failure patients showed that increased serum uric acid level (>8.7 mg/dL) carried even stronger prognostic information than N-terminal pro-B-type natriuretic peptide (NT-proBNP) on cardiac events (composite of cardiac death and hospitalization for heart failure.[18] For clinical use as a disease marker it would be desirable to establish one or several cut-off points for UA levels in CHF patients that provide clear guidance as to increasing risk. No such limits are currently available. Several aspects need to be discussed in this context. The range of normal physiologic values of UA is genderdependent and follows a Gaussian distribution with slightly higher values in men than in women. The cut-off points for hyperuricemia as currently applied in studies are based on (gender-independent) limits of serum solubility of UA in which precipitation of UA (ie, acute gout) becomes imminent. Although useful in gout patients,

these limits may not be applicable to reflect the association of UA with morbidity and mortality in HF patients. Several cut-off points for UA levels have been proposed for HF populations based on findings in individual study populations. They range from 6.5 mg/dL or higher in patients with mild to moderate HF14 to 8.7 mg/dL18 and 9.5 mg/dL12 in patients with more advanced CHF and from 7.0 mg/dL15 to 7.7 mg/dL in patients with acute HF.16 Further work is needed to establish and validate a more consistent grading system for hyperuricemia to improve clinical applicability of UA as a disease marker.

HYPERURICEMIA: ACTIVE PLAYER OR MERE MARKER IN THE DISEASE PROCESS?

It is a matter of ongoing debate whether UA itself has a functional role in the pathophysiology of heart failure or whether it is a mere marker of disease progression without functional involvement. In general, the finding of UA to predict outcome in patients with CHF does not presume a causal contribution from UA, nor would this be a requirement to use UA as a prognostic marker. The former perception of UA as a metabolically inert final step of purine degradation has changed because recent evidence suggests a significant role of this enzymatic pathway and of UA itself within metabolic and immunologic regulation. UA has been identified as a principal endogenous danger signal to cell injury that activates cellular immune response.[19] It is produced constitutively in cells of all tissues and increasingly is released when cells are injured to stimulate dendritic cell maturation and T-cell response. This is in line with previous observations that infusion of UA in a mouse model triggered increased production of tumor necrosis factor-α on endotoxin stimulation.[20] In addition, other direct effects of UA have been observed such as promotion of low-density lipoprotein (LDL) oxidation[21] and in vitro smooth muscle cell proliferation.[22] To what degree these findings have a relevant impact in patients with CVD needs to be established. Much more evidence has emerged to suggest UA as a marker of an up-regulated activity of the enzyme xanthine oxidase (XO). This is discussed in more detail in the following section. XO has been established as a major source of reactive oxygen species (ROS) and hence as an originator of a wealth of detrimental effects in various acute and chronic disease conditions including CVD. The complexity of the role of UA is complicated further because UA is an abundant antioxidant that accounts for much of

the protective free radical scavenging capacity in human plasma.[23] Infusion of UA has been observed to increase antioxidant capacity and to decrease oxidative stress in healthy subjects.[24] Accordingly, a protective function of hyperuricemia has been suggested for heart failure patients.[25] This discussion is inseparably linked with the examination of the mechanisms of increased UA levels in CHF patients. A dependency of increased UA levels on impaired renal function is often pointed out and increasing UA levels therefore are discussed by some (see comment above) to be merely a reflection of impaired renal function. Indeed, renal impairment is frequent in CHF and UA excretion depends on renal function and might be compromised further by diuretic treatment in these patients. Several lines of evidence suggest, however, that hyperuricemia in these patients results from increased purine degradation from tissue turnover and from diversion of metabolites that are triggered by several factors including tissue hypoxia, [26] catabolism,10 insulin resistance, [27] and cell death. Increased substrate supply and direct stimulation such as from inflammatory cytokines and oxygen radicals[28] accounts for up-regulated activity of the XO catabolic pathway as the predominating mechanism of hyperuricemia in CHF (Fig. 2).[29] On this basis, overproduction rather than undersecretion is the underlying principle of hyperuricemia in CHF. First, direct assessment of XO has shown increased enzymatic activity in CHF.[30-32] Second, treatment studies aimed at inhibition of XO showed several clinical benefits whereas therapies that decreased UA directly by increased renal excretion or by UA degradation did not yield comparable effects. This is discussed in detail later. The widely adopted current position in this discussion is that UA levels may indeed be more of a marker than an active player within the pathophysiology of CHF because UA reflects up-regulated XO activity. However, assessing serum UA is, opposite of direct assessment of XO, a widely available, well-standardized, simple, and inexpensive laboratory measurement. Given the powerful prognostic implication obtained from UA levels, it has many of the desired characteristics of an ideal biomarker for evaluation of CHF patients.

XO AS A SOURCE OF FREE OXYGEN RADICAL PRODUCTION

A substantial body of evidence has established the oxygen radical– generating capacity of the UA-producing enzyme XO as a pivotal pathophysiologic feature of CVD. In fact, in 1968 cytosolic XO was the first documented biological system shown to produce oxygenderived free radicals.[33] XO produces free oxygen radicals in

stoichiometric quantities along with UA and is one of the major sources of oxygen radical production in human physiology. For each oxidative step of hypoxanthine and xanthine two electrons are transferred to XO and the fully reduced XO^{6e-} yields the production of two H2O2 and two $O2^{-}$.[34] ROS accumulation accounts for a number of detrimental effects in CVD such as endothelium dysfunction, [35] impaired myocardial contractility, inflammatory activation, metabolic imbalance, and others. Notably, the enzyme xanthine oxidoreductase exists in two interconvertible forms, that is, xanthine dehydrogenase (XDH; EC 1.17.1.4) and XO (EC 1.17.3.2). Although UA is the enzymatic product of both forms, the XDH form has NAD^{+} as the preferred redox partner whereas in the oxidase form the enzyme is using oxygen as an electron acceptor, thus producing reactive oxygen species, mainly superoxide anion and H2O2 (Fig. 3). XDH is the predominant form in well-oxygenized tissue[36] but readily is converted to XO under various conditions. [37,38] In turn, hypoxia/ischemia favors XDH to XO conversion, which is a common condition in CVD patients. Notably, circulating XO can bind to the endothelium surface where its induced ROS-producing capacity significantly contributes to further endothelial injury.[39] Accordingly, in coronary arteries from patients with coronary artery disease (CAD) an increase of XO protein and its activity, but not of xanthine dehydrogenase protein levels, recently has been observed.[40,41] Increased endothelium-bound XO activity has been shown in CHF patients.31 Moreover, a redox-sensitive activation of endothelial XO activity is suggested from the observation that NAD(P)H oxidase– derived ROS production further stimulates XO-derived superoxide production in endothelial cells.[42] Although UA is produced in all tissues throughout the body, the highest activity of XO (apart from the lactating mammary glands) has been observed in the capillary endothelial cells[43] of the intestine and the liver.36 Given this specific distribution and the toxic effects of ROS, a role as a defense mechanism has been suggested, such as to protect the inner surface (ie, the barrier between intestinal lumen and the body tissues) from an infectious pathogen invasion.[44] It is a common pathophysiologic mechanism in human biology that well-tuned adaptive mechanisms intended as response to short-term injury may turn into maladaptive processes and lead eventually to harmful effects when activated in the long term such as in chronic disease conditions. The protective antioxidant capacity of UA then may act as a negative feedback principle leading to continued ROS accumulation with deleterious effects including increased cytokine production, [45] cell apoptosis,[46] and endothelial dysfunction,[47] all of which occur in chronic

diseases. It has been shown that endothelium-bound XO activity and protein levels are increased substantially in patients with coronary disease, 40,41 carotid stenosis,[48] or chronic heart failure,30,31 and are related inversely to endothelium-dependent vasodilation. 40

XO-DERIVED ROS: IMPACT IN CVD

A substantial body of evidence has accumulated showing a pathophysiologic involvement of increased XO activity in CVD. Increased ROS production, in particular superoxide anions, interacts readily with endothelium-derived NO to form peroxynitrite (ONOO-, in itself a highly active oxygen radical), starting a cascade of detrimental oxygen radical effects.[49] ROS accumulation has been suggested as a major cause of endothelial dysfunction in both experimental and clinical studies with CAD42 in CHF.[50] Besides impaired myocardial and peripheral tissue perfusion, direct effects on myocardial and skeletal metabolic and functional capacity result from an increase in ROS accumulation in CVD. Consequently, the therapeutic approach of XO inhibition seems to be an intriguing concept to counteract a range of these processes. Indeed, several studies have observed an improved endothelium-dependent vasodilation after allopurinol or oxypurinol therapy in patients with CAD or CHF.[50-52] An indirect effect of allopurinol on regulation of vascular tone via interaction with asymmetric dimethylarginine has been observed.[53] In addition, multiple other pathophysiologic features in CVD were shown to be improved after XO inhibition (Table 1). From those proof-of-concept studies, further evidence has emerged that indeed XO activity rather than UA may be viewed as the true therapeutic target. Direct UA decreases with different approaches but without inhibition of XO was observed in several studies as ineffective to prevent detrimental effects seen in hyperuricemic patients. In these studies renal reabsorption inhibitors benzbromarone[54] and probenecid[55] were used to increase UA excretion, or the enzyme urate oxidase was used to promote the further degradation of UA to allantoin.[56] UA levels were reduced with these therapies by 34%, 46%, and 64%, respectively, which compares and even exceeds the UA lowering effect of allopurinol in these patients. All three approaches failed, however, to improve endothelium function or other measures of clinical status.

XO INHIBITION: A NOVEL THERAPY OPTION IN CVD?

Treatment effects on CVD as outlined earlier showed beneficial effects in both animal models and clinical studies on various clinical and biochemical variables such as myocardial perfusion and contractility, peripheral vascular resistance, afterload, and BNP levels (Table 1). Although therapeutic effects on those surrogate markers of CVD are promising, the proof of XO inhibition as a valuable novel therapeutic approach would depend on evidence of improved mortality or clinically meaningful measures of morbidity. A large retrospective cohort study including 4,785 patients with CHF investigated the effect of allopurinol therapy on all-cause mortality in CHF patients with hyperuricemia.[57] It was observed that highdose (sufficient) XO inhibition therapy with allopurinol resulted in a survival benefit as compared with insufficient (low-dose) XO inhibition in the hyperuricemic CHF subjects (hazard ratio, 0.65; 95% CI, 0.42-0.99). A comparison with an allopurinol-free normo-uricemic control group was considered unsuitable for this study because mortality risk is a priori substantially increased in patients with increased UA levels (Fig. 1). One prospective study has been undertaken so far to test the impact of XO inhibition on mortality in CHF.[58] In this study, the OPT-CHF trial (impact of oxypurinol in patients with symptomatic heart failure), oxypurinol, the active metabolite of allopurinol, was used because it was considered superior to allopurinol. Allopurinol itself is a pro-drug that is converted into oxypurinol by XO in a superoxide radical– generating enzymatic step.[59] Despite the convincing pathophysiologic concept and intriguing data from preclinical and pilot clinical trials, the study failed to show a benefit on the composite primary end point of HF clinical status and mortality. This disappointing result likely may diminish the interest in further studies in this field. However, some aspects of the study design need to be discussed. Importantly, effective treatment effects may be expected only in patients in whom up-regulated activity of XO is truly apparent. As outlined earlier, the presence of hyperuricemia would be required as an indicator of high XO activity in CHF patients. Accordingly, in previous proof-of-concept treatment trials, effects were particularly observed in hyperuricemic patients.[50,51,60] By contrast, this treatment approach repeatedly failed in patients with normal UA levels (Fig. 4). The OPT-CHF trial enrolled patients without screening for UA levels. Notably, in this trial the anticipated results were indeed observed only when those patients with increased UA levels (≥9.5 mg/dL) were analyzed. This subgroup analysis, however, was lacking the power and prospective character of the overall study analysis. It might be concluded

that XO inhibition as a novel metabolic treatment approach in CHF might be suitable only in patients in whom increased UA levels are an indicator of up-regulated XO activity. Extending this approach to patients with normal UA levels might increase the number of nonresponders.[61] XO inhibition by allopurinol may as well be of interest in patients with CAD and stable angina pectoris. In a recent randomized controlled study of 65 patients with CAD and stable angina pectoris allopurinol therapy (600 mg/d) significantly delayed the onset of ST-segment depression in the ECG and increased total exercise time and time to chest pain in a symptom-limited treadmill exercise test (Bruce protocol).[62] Notably, time to ST depression and total exercise time were increased to a similar extent as has been observed for anti-anginal medications in clinical use, such as nitrates, calcium antagonists, ß-blockers, and ivabradine. The underlying mechanisms for the potential antiischemic properties of allopurinol remain to be examined further. Previous studies have suggested that allopurinol reduces myocardial oxygen consumption and improves myocardial efficacy.[63,64] Furthermore, effects to restore endothelial function after allopurinol or oxypurinol may contribute to reduced ischemia during exercise in CAD patients.[42,52] Notably, a dose-response relationship has been observed between allopurinol and its effect on endothelial function.[55] This raises the possibility that high- dose allopurinol treatment may be required to exert antiischemic effects in patients with coronary disease. However, more data from larger studies will be needed to confirm the anti-anginal effects of allopurinol and to compare the efficacy with other established anti-anginal therapies. Allopurinol, after all, is burdened with substantial side effects such as severe skin reactions and renal impairment. Whether oxypurinol or newer compounds with less side effects such as febuxostat, a noncomparative selective XO inhibitor,[65] may be better options for this targeted XO inhibition in CVD awaits further investigation.

SUMMARY

Hyperuricemia is a common finding in patients with CVD. It often is associated with the metabolic cluster within the metabolic syndrome. The discussion on the impact of UA as an independent risk factor in the normal population is ongoing but recent data suggest that it is unlikely that UA will significantly enhance the prediction of CVD in the general population. Among patients with established cardiac diseases, however, increased UA levels have been shown to be a powerful and reliable marker of advanced symptomatic disease state and a particularly poor prognosis. Assessment of

serum UA is a simple and nonexpensive laboratory measurement that ensures wide clinical availability. It has many of the desired characteristics of an ideal biomarker and should be assessed more regularly in cardiovascular patients, particularly in patients with CHF. Current evidence suggests that UA is more of a disease marker than an active player within the cardiovascular pathophysiology because high UA levels reflect up-regulated XO activity. The XO-derived ROS accumulation leads to NO scavenging and endothelium dysfunction but also to a variety of other detrimental metabolic, functional, and immunologic effects. Novel data are emerging to suggest as well direct effects of UA on immune stimulation and metabolic interference. In turn, UA has strong anti-oxidative potential and further work is needed to untangle the complex and at times conflicting interactions of UA. Recent clinical studies on the therapeutic effect of XO inhibition have suggested that XO inhibition could have a role as a tailored treatment option in hyperuricemic patients with CHF but may be unsuitable for nonselective use. Whether it may be applicable in CAD patients with stable angina to increase exercise endurance needs to be confirmed in further studies. Novel compounds for XO inhibition with more specific effects and less side effects may be a promising option to further explore the potential of this metabolic treatment in patients with CVD.

REFERENCES

1. Vuorinen-Markkola H, Yki-Jarvinen H. Hyperuricemia and insulin resistance. J Clin Endocrinol Metab. 1994;78:25-9.
2. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med. 2008;359:1811-21.
3. Reaven GM. Role of insulin resistance in human disease (syndrome X): an expanded definition. Annu Rev Med. 1993;44:121-31.
4. Wheeler JG, Juzwishin KD, Eiriksdottir G, Gudnason V, Danesh, J. Serum uric acid and coronary heart disease in 9,458 incident cases and 155,084 controls: prospective study and meta-analysis. PLoS Med. 2005;2:e76.
5. Holme I, Aastveit AH, Hammar N, et al. Uric acid and risk of myocardial infarction, stroke and congestive heart failure in 417 734 men and women in the Apolipoprotein MOrtality RISk study (AMORIS). J Intern Med. 2009;266:558-70.
6. Strasak AM, Kelleher CC, Brant LJ, et al. VHM&PP study group. Serum uric acid is an independent predictor for all major forms of cardiovascular death in 28,613 elderly women: a prospective 21-year follow-up study. Int J Cardiol. 2008;125:232-9.
7. Wong KY, MacWalter RS, Fraser HW, Crombie I, Ogston SA, Struthers AD. Urate predicts subsequent cardiac death in stroke survivors. Eur Heart J. 2002;23:788-93.
8. Ioachimescu AG, Brennan DM, Hoar BM, et al. Serum uric acid is an independent predictor of all-cause mortality in patients at high risk of cardiovascular disease: a preventive cardiology information system (PreCIS) database cohort study. Arthritis Rheum. 2008;58:623-30.
9. Dunkelgrun M, Welten GM, Goei D, et al. Association between serum uric acid and perioperative and late cardiovascular outcome in patients with suspected or definite coronary artery disease undergoing elective vascular surgery. Am J Cardiol. 2008;102: 797-801.
10. Doehner W, Rauchhaus M, Florea VG, Sharma R, Bolger AP, Davos CH, et al. Uric acid in cachectic and non-cachectic CHF patients—relation to leg vascular resistance. Am Heart J. 2001; 141:792-9.
11. Leyva F, Anker SD, Swan JW, Godsland IF, Wingrove CS, Chua TP, et al. Serum uric acid as an index of impaired oxidative metabolism in chronic heart failure. Eur Heart J. 1997;18:858-65. 12. Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. Circulation. 2003;107:1991-7.
13. Thanassoulis G, Brophy JM, Richard H, Pilote L. Gout, allopurinol use, and heart failure outcomes. Arch Intern Med. 2010;170: 1358-64. 14. Jankowska EA, Ponikowska B, Majda J, et al. Hyperuricaemia predicts poor outcome in patients with mild to moderate chronic heart failure. Int J Cardiol. 2007;115:151-5.
15. Pascual-Figal DA, Hurtado-Martínez JA, Redondo B, et al. Hyperuricaemia and long-term outcome after hospital discharge in acute heart failure patients. Eur J Heart Fail. 2007;9:518-24.
16. Alimonda AL, Núñez J, Núñez E, et al. Hyperuricemia in acute heart failure. More than a simple spectator? Eur J Intern Med. 2009;20:74-9.
17. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation. 2006;113:1424-33.
18. Kim H, Shin HW, Son J, Yoon HJ, Park HS, Cho YK, et al. Uric acid as prognostic marker in advanced nonischemic dilated cardiomyopathy: comparison with N-terminal pro B-type natriuretic peptide level. Congest Heart Fail. 2010;16:153-8.

19. Shi Y, Evans JE, Rock KL. Molecular identification of a danger signal that alerts the immune system to dying cells. Nature. 2003;425:516-21.
20. Netea MG, Kullberg BJ, Blok WL, et al. The role of hyperuricemia in the increased cytokine production after lipopolysaccharide challenge in neutropenic mice. Blood. 1997;89:577-82.
21. Bagnati M, Perugini C, Cau C, Bordone R, Albano E, Bellomo G. When and why a water-soluble antioxidant becomes pro-oxidant during copper-induced low-density lipoprotein oxidation: a study using uric acid. Biochem J. 1999;340:143-52.
22. Rao GN, Corson MA, Berk BC. Uric acid stimulates vascular smooth muscle cell proliferation by increasing platelet-derived growth factor A-chain expression. J Biol Chem. 1991;266:8604-8.
23. Maxwell SR, Thomason H, Sandler D, Leguen C, Baxter MA, Thorpe GH, et al. Antioxidant status in patients with uncomplicated insulin-dependent and non-insulin-dependent diabetes mellitus. Eur J Clin Invest. 1997;27:484-90.
24. Waring WS, Convery A, Mishra V, Shenkin A, Webb DJ, Maxwell SR. Uric acid reduces exercise-induced oxidative stress in healthy adults. Clin Sci (Lond). 2003;105:425-30.
25. Alcaino H, Greig D, Chiong M, Verdejo H, Miranda R, Concepcion R, et al. Serum uric acid correlates with extracellular superoxide dismutase activity in patients with chronic heart failure. Eur J Heart Fail. 2008;10:646-51.
26. Leyva F, Chua TP, Anker SD, Coats AJ. Uric acid in chronic heart failure: a measure of the anaerobic threshold. Metabolism. 1998;47:1156-9.
27. Leyva F, Wingrove CS, Godsland IF, Stevenson JC. The glycolytic pathway to coronary heart disease: a hypothesis. Metabolism. 1998;47:657-62.
28. Ashraf M, Samra ZQ. Subcellular distribution of xanthine oxidase during cardiac ischemia and reperfusion: an immunocytochemical study. J Submicrosc Cytol Pathol. 1993;25:193-201.
29. Doehner W, von Haehling S, Anker SD. Uric acid as a prognostic marker in acute heart failure—new expectations from an old molecule. Eur J Heart Fail. 2007;9:437-9.
30. Bakhtiiarov ZA. [Changes in xanthine oxidase activity in patients with circulatory failure]. (Article in Russian). Ter Arkh. 1989;61: 68-9.
31. Landmesser U, Spiekermann S, Dikalov S, Tatge H, Wilke R, Kohler C, et al. Vascular oxidative stress and endothelial dysfunction in patients with chronic heart failure: role of xanthineoxidase and extracellular superoxide dismutase. Circulation. 2002;106:3073-8.
32. Doehner W, Tarpey MT, Pavitt DV, Bolger AP, Wensel R, von Haehling S, et al. Elevated plasma xanthine oxidase activity in chronic heart failure: source of increased oxygen radical load and effect of allopurinol in a placebo controlled, double blinded treatment study. J Am Coll Cardiol. 2003;42(Suppl):207A.
33. McCord JM, Fridovich I. The reduction of cytochrome c by milk xanthine oxidase. J Biol Chem. 1968;243:5753-60.
34. Hille R, Massey V. Studies on the oxidative half-reaction of xanthine oxidase. J Biol Chem. 1981;256:9090-5.
35. Landmesser U, Hornig B, Drexler H. Endothelial function: a critical determinant in atherosclerosis? Circulation. 2004;109(Suppl 1): II27-33.
36. Sarnesto A, Linder N, Raivio KO. Organ distribution and molecular forms of human xanthine dehydrogenase/xanthine oxidase protein. Lab Invest. 1996;74:48-56.

37. Stirpe F, Della Corte E. The regulation of rat liver xanthine oxidase. Conversion in vitro of the enzyme activity from dehydrogenase (type D) to oxidase (type O). J Biol Chem. 1969;244: 3855-63.
38. Nishino T, Okamoto K, Eger BT, Pai EF. Mammalian xanthine oxidoreductase—mechanism of transition from xanthine dehydrogenase to xanthine oxidase. FEBS J. 2008;275:3278-89.
39. Houston M, Estevez A, Chumley P, Aslan M, Marklund S, Parks DA, et al. Binding of xanthine oxidase to vascular endothelium. Kinetic characterization and oxidative impairment of nitric oxidedependent signaling. J Biol Chem. 1999;274:4985-94.
40. Spiekermann S, Landmesser U, Dikalov S, Bredt M, Gamez G, Tatge H, et al. Electron spin resonance characterization of vascular xanthine and NAD(P)H oxidase activity in patients with coronary artery disease: relation to endothelium-dependent vasodilation. Circulation. 2003;107:1383-9.
41. Guzik TJ, Sadowski J, Guzik B, Jopek A, Kapelak B, Przybylowski P, et al. Coronary artery superoxide production and nox isoform expression in human coronary artery disease. Arterioscler Thromb Vasc Biol. 2006;26:333-9.
42. Landmesser U, Spiekermann S, Preuss C, Sorrentino S, Fischer D, Manes C, et al. Angiotensin II induces endothelial xanthine oxidase activation: role for endothelial dysfunction in patients with coronary disease. Arterioscler Thromb Vasc Biol. 2007;27:943-8.
43. Jarasch ED, Grund C, Bruder G, Heid HW, Keenan TW, Franke WW. Localization of xanthine oxidase in mammary-gland epithelium and capillary endothelium. Cell. 1981;25:67-82.
44. Tubaro E, Lotti B, Cavallo G, Croce C, Borelli G. Liver xanthine oxidase increase in mice in three pathological models. A possible defense mechanism. Biochem Pharmacol. 1980;29:1939-43.
45. Bolger AP, Anker SD. Tumour necrosis factor in chronic heart failure: a peripheral view on pathogenesis, clinical manifestations and therapeutic implications. Drugs. 2000;60:1245-57.
46. Adams V, Jiang H, Yu J, et al. Apoptosis in skeletal myocytes of patients with chronic heart failure is associated with exercise intolerance. J Am Coll Cardiol. 1999;33:959-65.
47. Hornig B, Maier V, Drexler H. Physical training improves endothelial function in patients with chronic heart failure. Circulation. 1996;93:210-4.
48. Patetsios P, Song M, Shutze WP, Pappas C, Rodino W, Ramirez JA, et al. Identification of uric acid and xanthine oxidase in atherosclerotic plaque. Am J Cardiol. 2001;88:188-91, A186
49. Maxwell AJ, Bruinsma KA. Uric acid is closely linked to vascular nitric oxide activity. Evidence for mechanism of association with cardiovascular disease. J Am Coll Cardiol. 2001;38:1850-8.
50. Doehner W, Schoene N, Rauchhaus M, Leyva-Leon F, Pavitt DV, Reaveley DA, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. Circulation. 2002;105:2619-24.
51. Farquharson CA, Butler R, Hill A, Belch JJ, Struthers AD. Allopurinol improves endothelial dysfunction in chronic heart failure. Circulation. 2002;106:221-6.
52. Baldus S, Koster R, Chumley P, Heitzer T, Rudolph V, Ostad MA, et al. Oxypurinol improves coronary and peripheral endothelial function in patients with coronary artery disease. Free Radic Biol Med. 2005;39:1184-90.

53. von Haehling S, Bode-Böger SM, Martens-Lobenhoffer J, Rauchhaus M, Schefold JC, Genth-Zotz S, et al. Elevated levels of asymmetric dimethylarginine in chronic heart failure: a pathophysiologic link between oxygen radical load and impaired vasodilator capacity and the therapeutic effect of allopurinol. Clin Pharmacol Ther. 2010;88:506-12.
54. Ogino K, Kato M, Furuse Y, Kinugasa Y, Ishida K, Shuichi Osaki S, et al. Uric acid lowering treatment with benzbromarone in patients with heart failure: a double blind placebo-controlled cross-over preliminary study. Circ Heart Fail. 2010;3:73-81.
55. George J, Carr E, Davies J, Belch JJ, Struthers A. High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. Circulation. 2006;114:2508-16.
56. Waring WS, McKnight JA, Webb DJ, Maxwell SR. Lowering serum urate does not improve endothelial function in patients with type 2 diabetes. Diabetologia. 2007;50:2572-9.
57. Wei L, Fahey T, Struthers AD, MacDonald TM. Association between allopurinol and mortality in heart failure patients: a long-term follow-up study. Int J Clin Pract. 2009;63:1327-33.
58. Hare JM, Mangal B, Brown J, et al. OPT-CHF Investigators. Impact of oxypurinol in patients with symptomatic heart failure. Results of the OPT-CHF study. J Am Coll Cardiol. 2008;51: 2301-9.
59. Galbusera C, Orth P, Fedida D, Spector T. Superoxide radical production by allopurinol and xanthine oxidase. Biochem Pharmacol. 2006;71:1747-52.
60. Mercuro G, Vitale C, Cerquetani E, Zoncu S, Deidda M, Fini M, et al. Effect of hyperuricemia upon endothelial function in pa- tients at increased cardiovascular risk. Am J Cardiol. 2004;94: 932-5.
61. Doehner W, Anker SD. Xanthine oxidase inhibition for chronic heart failure: is allopurinol the next therapeutic advance in heart failure? Heart. 2005;91:707-9.
62. Noman A, Ang DS, Ogston S, Lang CC, Struthers AD. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial. Lancet. 2010;375:2161-7.
63. Ekelund UE, Harrison RW, Shokek O, Thakkar RN, Tunin RS, Senzaki H, et al. Intravenous allopurinol decreases myocardial oxygen consumption and increases mechanical efficiency in dogs with pacing-induced heart failure. Circ Res. 1999;85:437- 45.
64. Cappola TP, Kass DA, Nelson GS, Berger RD, Rosas GO, Kobeissi ZA, et al. Allopurinol improves myocardial efficiency in patients with idiopathic dilated cardiomyopathy. Circulation. 2001;104:2407-11.
65. Becker MA, Schumacher HR Jr, Wortmann RL, MacDonald PA, Eustace D, Palo WA, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med. 2005; 353:2450-61.
66. Doehner W, von Haehling S, Anker SD. Uric acid in CHF: marker or player in a metabolic disease? Int J Cardiol. 2007; 115:156-8.
67. Ukai T, Cheng CP, Tachibana H, Igawa A, Zhang ZS, Cheng HJ, et al. Allopurinol enhances the contractile response to dobutamine and exercise in dogs with pacing-induced heart failure. Circulation. 2001;103:750-5.
68. Coghlan JG, Flitter WD, Clutton SM, et al. Allopurinol pretreatment improves postoperative recovery and reduces lipid peroxidation in patients undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg. 1994;107:248-56.
69. Waikakul S, Unnanantana A, Vanadurongwan V. The role of allopurinol in digital replantation. J Hand Surg. 1999;24B:325-7.

70. Engberding N, Spiekermann S, Schaefer A, Heineke A, Wiencke A, Muller M, et al. Allopurinol attenuates left ventricular remodeling and dysfunction after experimental myocardial infarction. Circulation. 2004;110:2175-9.
71. Cingolani HE, Plastino JA, Escudero EM, Mangal B, Brown J, Pérez NG. The effect of xanthine oxidase inhibition upon ejection fraction in heart failure patients: La Plata Study. J Card Fail. 2006;12:491-8.
72. Shadid M, Van Bel F, Steendijk P, Dorrepaal CA, Moison R, Van der Velde ET, et al. Pretreatment with allopurinol in cardiac hypoxic-ischemic reperfusion injury in newborn lambs exerts its beneficial effect through afterload reduction. Basic Res Cardiol. 1999;94:23-30.
73. Gavin AD, Struthers AD. Allopurinol reduces B-type natriuretic peptide concentrations and haemoglobin but does not alter exercise capacity in chronic heart failure. Heart. 2005;91:749-53.

Figures

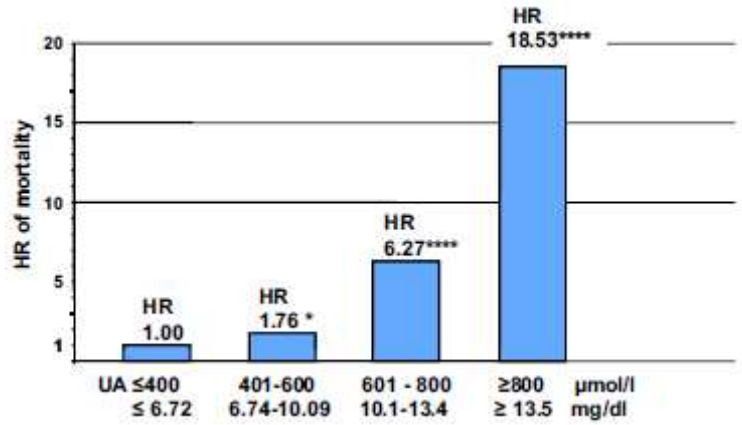


Figure 1. Graded relationship of serum UA and survival in CHF patients. UA ≥ 400 µmol/L = 6.72 mg/dL as reference group (HR, 1). *P < .05 and ****P < .0001 vs referent. Adapted from Anker and Doehner et al.[12]

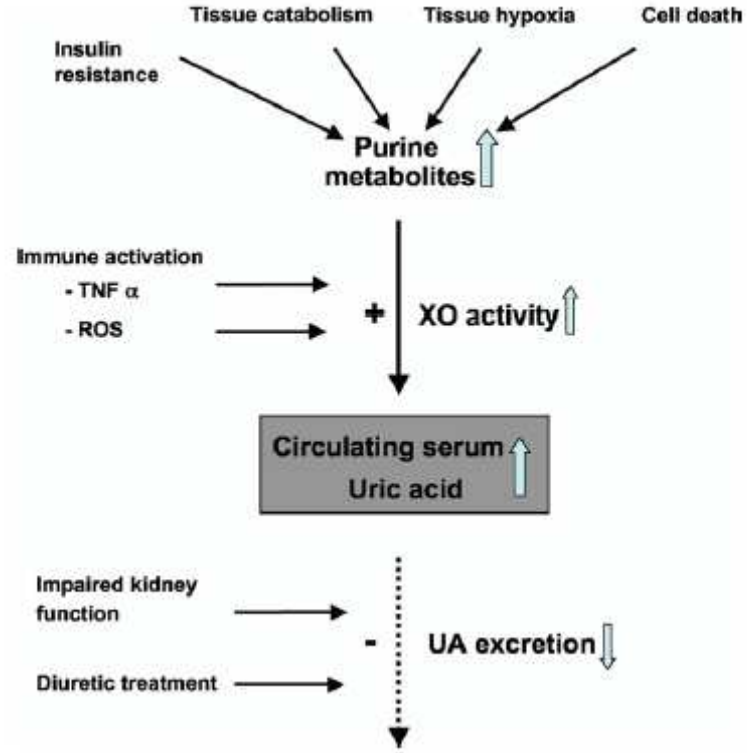


Figure 2. Increased serum UA levels in CHF origin from a combination of overproduction and from undersecretion. TNFα, tumor necrosis factor α. Adapted from Doehner et al.[29]

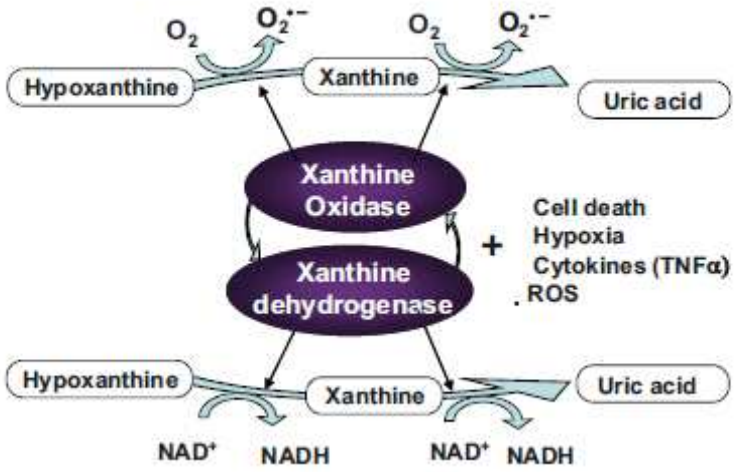
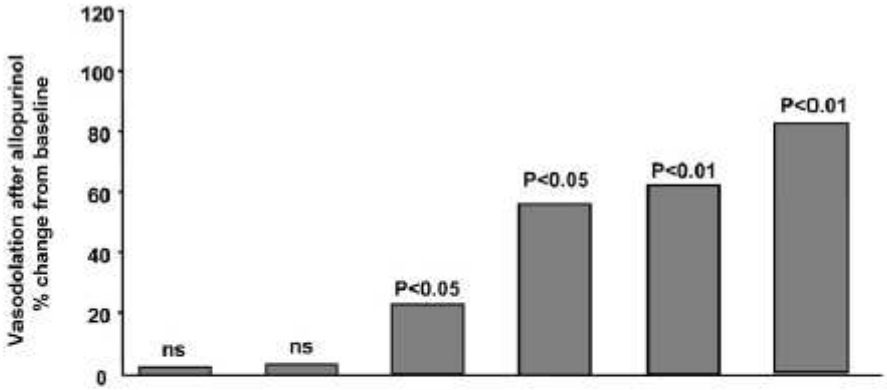


Figure 3. Xanthine oxidoreductase (XOR; EC 1.17.3.2) exists in two interconvertible forms that use either NAD^+ (XDH) or oxygen (XO) as redox partner. TNFα, tumor necrosis factor α.



Study	[50]	[60]	[50]	[50]	[51]	[60]
	Normal uric acid levels at enrolment		Elevated uric acid levels			
treatment period	acute	3 months	acute	1 week	1 month	3 months
Allopurinol	600 µg/min	300 mg/d	600 µg/min	300 mg/d	300 mg/d	300 mg/d
Baseline UA (µmol/L)	315±42	321±22	535±54	558±21	420±80	553±16

Figure 4. Efficacy of treatment with XO inhibitors depends on UA levels at enrollment. Positive effects were observed in studies with increased UA levels whereas no effect was seen if UA levels were normal. Adapted from Doehner et al.[62]

Table 1. Increased UA Level Is Associated With a Range of Pathophysiologic Surrogate Markers in CVD: Therapeutic Inhibition of XO Has Been Shown to Attenuate These Processes

Pathophysiologic Surrogate	Improvement on XO Inhibition
Myocardial mechanical efficiency ↓	Ekelund et al,[63] 1999
Myocardial energy efficiency ↓	Cappola et al,[64] 2001
Myocardial contractility ↓	Ukai et al,[67] 2001
Myocardial reperfusion injury	Coghlan et al,[68] 1994
Peripheral reperfusion injury	Waikakul et al,[69] 1999
Myocardial remodeling ↑	Engberding et al,[70] 2001
LV ejection fraction ↓	Cingolani et al,[71] 2006
Cardiac afterload ↑	Shadid et al,[72] 1999
Endothelium dysfunction ↑	Farquharson et al,[51] 2002
Peripheral tissue perfusion ↓	Doehner et al,[50] 2002
Plasma BNP level ↑	Gavin and Struthers,[73] 2005
CHF disease progression ↑	Wei et al,[57] 2009

Abbreviations: LV, left ventricular; BNP, brain natriuretic peptide.
Data from Doehner et al.[66]